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Liu, Liang Q. ORCID logoORCID: <https://orcid.org/0000-0002-6358-1637>, Moody, Julie and Gall, Angela (2015) Do electrical stimulation enhance pressure ulcer healing in people living with spinal cord injuries: a meta-analysis and systematic review of randomised and non-randomised controlled trials. In: 25th Conference of the European Wound Management Association (EWMA 2015), 13-15 May 2015, ExCeL London, UK. . [Conference or Workshop Item]

First submitted uncorrected version (with author's formatting)

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Do Electrical Stimulation Enhance Pressure Ulcer Healing in People living with Spinal Cord Injuries: A Meta-Analysis and Systematic Review of Randomised and Non-Randomised Controlled Trials

ABSTRACT

Context: Electrical stimulation (ES) can confer benefit to chronic wound healing. However, clinical guidelines regarding the use of ES for pressure ulcer (PrU) management in spinal cord injuries (SCI) remain to be limited.

Objectives: To quantitatively analyse the effect of ES on PrU healing compared with standard wound care (SWC) and/or sham stimulation.

Method: Review was limited to peer-reviewed studies published in English from 1970 to May 2014. Studies included randomized controlled trials (RCTs) and non-RCTs. Pooled analyses were performed to calculate mean difference (MD) for continuous data, odds ratio (OR) for dichotomous data. Eight prospective controlled studies were reviewed, five studies were RCTs, and three studies were non-RCTs. Pooled analyses of eight trials showed ES significantly improved daily healing rate (MD 0.89, 95% CI 0.23-1.55, $p=0.008$) with significant heterogeneity. Pulsed current ES significantly improved daily healing rates compared with constant direct current (DC) or alternating current (AC) in two trials (MD 1.50, 95% CI 0.62, 2.39, $p=0.0009$, $I^2=81\%$). Pooled analysis of two trials showed significant higher numbers of ulcer healed (OR 2.95, 95% CI 1.69–5.17, $p=0.0002$, $I^2=0\%$) with ES treatment. There was a trend towards less number of ulcer worsened with ES treatment (OR 0.38, 95% CI 0.12–1.24, $p=0.11$, $I^2=18\%$). intervals (CI).

Results:

Conclusion: ES can significantly enhance PrU healing in SCI according to limited level I evidence. Pulsed current ES may confer better benefit on PrU healing than DC or AC. Electrodes placed on wound bed maybe superior to those applied on the intact skin.

KEY WORDS

Electrical stimulation, pressure ulcer, spinal cord injury, systematic review, meta-analysis

ABBREVIATION

CI Confidence interval

ES Electrical Stimulation
ITT Intention to treat
MD Mean difference
OR Odd ratio
PrU Pressure ulcer
RCT Randomized Controlled Trial
SCI Spinal Cord Injury
SWC Standard wound care

INTRODUCTION

Pressure ulcer is one of the most common secondary complications following Spinal Cord Injury. According to the Model SCI System Statistical Centre, the annual incidence rate of PUs is seen at 14.7% in the first post-injury year and noted to be steadily increasing thereafter¹. It is estimated that up to 85% people living with SCI develop a pressure ulcer during their life time²⁻⁴.

Once a PrU is developed, it significantly increases SCI individual and/or the caregivers' burden, and has substantial detrimental impact on the quality of life, independence, and dignity of a patient⁵⁻⁷. If a PrU is severe, it can lead to further disabilities, need for surgical interventions and even fatal infections.⁷ Apart from personal consequences, PrU also represent a significant cost burden for health and social care systems. Treating a PU varies from £1,214 (Category I) to £14,108 (Category IV) in the United Kingdom, with a total annual cost being £1.4-£2.1 billion⁸ for the treatment.

According to National/European Pressure Ulcer Advisory Panel (NPUAP/EPUAP), a PrU is described as an area of localised damage to the skin as a result of prolonged pressure alone, or pressure in combination with shearing forces⁵. It is typically categorised into four key stages depending on the age and severity. So far, once a PrU is diagnosed, conventional standard nursing care will be provided, which includes offloading, improving nutrition, revascularization, compression, and/or debridement. Generally, it is predicted that the ulcer should completely heal if a 50% reduction in ulcer size achieved by 4 weeks of treatment in the absence of infection. If this reduction in size cannot be achieved, the ulcer is likely to

have stagnated into a chronic phase, then advanced therapies will usually be advocated to speed up the healing process.⁹ A number of advanced treatments are documented in the literature, such as bioengineered skin substitutes, negative pressure wound devices, oxygen, ultrasound and electrical stimulation. Determining which of the advanced therapies to use, it often depends on availability of modalities and the cost and time invested⁹.

Electrical stimulation to enhance healing of various chronic wounds including pressure ulcers in spinal cord injured individuals has been reported in the literature for decades¹⁰⁻¹². A recent systematic review suggested that ES is cost effective for treating PUs in SCI¹³, yet clinical practice guidelines regarding the use of ES for PU treatment in SCI remain limited^{14,15}. The lack of consistence in the use of stimulation mode, parameters and clinical outcomes together with the small sample size in the individual published trial make health professionals and health providers difficult to make clinical decision on the implement of ES treatment for PrU.

Most recently, we conducted a systematic review of all types of studies to synthesize the evidence of ES on PU prevention and treatment in SCI, in which we descriptively reported type of ES device, electrical stimulation parameters in both prevention and treatment categories. However, a quantitative meta-analysis of the effectiveness of ES on PU healing was not performed. Meta-analysis that quantitatively calculates weighted averages of findings across multiple trials can increase the statistical power of the existing small sample size of individual studies. With the purpose of obtaining a better understanding of how different mode of ES enhance PrU healing, this updated systematic review was therefore conducted to to quantify the effect of ES on PU healing in SCI.

The primary aim of the study was to establish the effectiveness of ES on the average daily healing rates and numbers of PrU completed healed when compared with SWC and/or sham stimulation. Subgroup analysis was performed to assess the effect of different type of ES current and location of electrodes placement on PrU healing in SCI. We also investigated the number of PrU worsened and any adverse event related ES treatment.

OBJECTIVES

The aims of this review were 1) to critically appraise the research evidence available on ES for treatment of PrU; 2) to quantify the effect of ES as an adjunctive therapy for PrU healing

in people living with SCI when compared to SWC and/or sham stimulation; 3) to explore whether different type of ES current and location of electrodes placement may have the influence on the effectiveness of ES.

The meta-analysis specifically estimated ES treatment effect on average daily changes of wound size and numbers of ulcers completely healed and worsened.

METHODS

Search Methods for Identification of Studies

An original systematic review protocol was registered in the PROSPERO database in July 2013 (<http://www.crd.york.ac.uk/PROSPERO/>) and the registration number is CRD42013005088. The author (LL) updated the search up to 3rd July 2014 by using the same search strategy that was published previously¹⁶. Full reports of RCTs and prospective non-RCTs were identified through searches of the Medline, Embase, CINAL, PsycINFO and the Cochrane Central Register of Controlled Trials without language restrictions. Search terms in each database together with other recourse were described in our original systematic review¹⁶.

Inclusion Criteria

For primary analysis, eligible studies included randomized controlled trials (RCTs) and non-randomized controlled trials in SCI that compared any type of ES as an adjunctive therapy with sham ES or without ES intervention. All studies had to report ulcer outcome measurement, e.g. wound size or average healing rate per day, per week or during whole study period.

Data extraction and methodological quality

The following data was extracted from eligible articles by one reviewer (LL) and cross-checked by the second reviewer (JM): year of publication, country of author affiliated and type of study design. All other data including sample size, participants' age, gender, type and level of SCI, the type of electric stimulation, period of the stimulation, pattern of stimulation, location of electrodes placement, following up duration, adverse events, outcome measures on percentage change in wound surface area or change in ulcer size along with methodological quality was assessed independently by two reviewers (LL&JM). Any

disagreement in assessed findings between the two independent reviewers was resolved by discussion or through consultation with a third reviewer.

A quality assessment was conducted for each article. For RCTs a Jadad score was used together with the item allocation concealment and whether the analysis was based on the randomized groups,^{16,17} and a modified Downs and Black tool for non-RCTs.^{15,18} Both scales are well-established tools for assessing and reporting on the quality of clinical and health-related studies in the literature.

Data analysis

Data were extracted by two reviewers (LL & JM) using a spreadsheet. A meta-analysis was performed to estimate the pooled ES treatment effect on daily healing rate, the number of ulcer healed and the incidence of ulcer worsened. Daily healing rate was defined as mean percentage changes in ulcer size per day. For those trials that calculated the healing rate weekly or during whole study period, the daily healing rate was calculated and used for pooled analysis. Review Manager (RevMan version 5.3) was used to pool the healing rate per day and numbers of ulcer completed healed and worsened among studies. We pooled all data irrespective of the length of treatment and follow-up. A subgroup analysis was performed for good quality RCTs. We also analysed the pooled treatment effect on healing rate using different types of stimulation current and location of electrodes placement. For trials with more than two arms, the changes of healing rate and number of ulcer healed or worsened were compared separately with the control arm (no ES/sham ES). Treatment effect was significant if $P < 0.05$. Heterogeneity between studies was tested with the use of both chi square test (significant if $P < 0.1$) and I^2 test (with substantial heterogeneity defined as values $> 50\%$). When studies showed significant heterogeneity, the Mantel–Haenszel random effects model was used to calculate mean difference. Otherwise, the fixed effects model was used to calculate the pooled effect sizes when studies did not show heterogeneity.

RESULTS

Included Studies

The literature search identified a total of 407 unique references that were all exported to Endnote (Endnote version X7 for Windows Thomson Reuters), and three additional articles were identified from other sources. Of these five hundreds articles, one hundred and seventeen were identified as duplicates, thus resulting in two hundred and eighty abstracts

and titles that were available for sifting for eligibility. All two hundred and eighty abstracts were further screened and this subsequently generated eighty abstracts that were potentially relevant. The full texts of these eighty abstracts were retrieved and considered for eligibility for inclusion in the final review. The outcome following this procedure was that a total of eight studies met the inclusion criteria and were subjected to full-data extraction and quantitative analysis. **Figure 1** provides a flow chart of the process and results for screening eligibility and study selection.

All 8 studies^{12,14,19-24} described the study target population as spinal cord injuries (SCI). Among the 8 studies, 5 trials were RCTs, other 3 trials were prospective non-randomized controlled trials. As a whole, the number of patients per study ranged from 7 to 106, with the number of ulcer range from 7 to 192. Four studies measured mean daily percentage change in ulcer size, one study measured mean weekly percentage change in ulcer size, and other 3 studies measured mean percentage change in ulcer size across whole study period. Details of sample characteristics are shown in **Table1**.

Methodological Quality

In a total of five RCTs, one trial described an appropriate method to generate the randomization sequence. Two studies were double-blinded and described the method of double-blinding, three trials adequately described allocation concealment and two trials used ‘intention to treat’ (ITT) to analyse the data. Two RCTs were considered to be of reasonably good methodological quality according to the Jadad score along with other two items, hence they were classified as low risk of bias trials. Three poor quality of RCTs were considered as moderate risk of bias. Three non-RCTs were assessed for their reporting quality using the Down and Black tool. The scores of these trials were 13, 8 and 4 out of a total achievable score of 28. These three non-RCTs therefore were considered as high risk of bias trials.

Data pooling and meta-analysis

Effectiveness of ES

1) Mean daily healing rate

- Overall healing rate: daily healing rate measured as mean percentage change per day in ulcer size. Pooled analyses of all eight trials showed that people receiving ES treatment in adjunction to standard wound care reported higher daily healing rate by 0.89% (8 trials with 12 comparisons, 95% CI 0.23-1.55, $p=0.008$), however,

heterogeneity was substantial ($I^2=91\%$, $p<0.00001$). A subgroup analysis of RCTs that were considered to be of good methodological quality also showed a higher daily healing rate in people treated with ES than people without ES treatment, but the pooled effect was not significant (MD 0.71, 95% CI -0.05, 1.47, $p=0.07$, $I^2=67\%$).

- Healing rate by pulsed current versus constant direct or alternating current: There were 5 trials compared pulsed current with sham ES/no ES, one trial compared pulsed current with sham ES/no ES, one trial applied constant direct current in both group but with different electrodes placement. There were 2 trials compared with pulsed current with constant direct or alternating current. Pooled analysis of these two trials showed that a significant higher healing rate in people treated with pulsed current ES than that those treated with constant or alternating current ES (MD 1.50, 95% CI (0.62, 2.39), $p=0.0009$). However, the heterogeneity was substantial ($I^2=81\%$).
- Healing rate by active electrode placed over the wound bed versus both electrodes placed on intact skin/ the edge of wound: One study²⁴ compared the effect of ES delivered by applying the electrodes either across the wound or on the intact skin around the ulcer. The daily healing rates of PrU treated with one electrode overlaid wound was higher than those with electrodes placed on intact skin (MD 2.60, 95% CI (1.55-3.65), $p<0.0001$). We performed a meta-analysis for 5 trials that applied the active electrodes across wound and found that a significant higher rate with ES than without ES (MD 0.88, 95% CI 0.62-1.15, $p<0.00001$), however the heterogeneity was substantial ($I^2=88\%$). Pooled analysis for 5 trials that applied both electrodes on the intact skin showed no significant difference in healing rate between people received ES and those who received standard wound care without ES (MD -0.07, 95% CI -0.34-0.19), $p=0.59$, $I^2=90\%$).

2) . Number of ulcer completely healed: two trials reported numbers of ulcer healed during study period. Pooled analysis of these 2 trials showed showed significant higher numbers of ulcer healed with ES treatment (OR 2.95, 95% CI 1.69–5.17, $p=0.0002$, $I^2=0\%$). .

3). Incidence of ulcer worsened: two studies reported the incidence of ulcer worsened during the study period. There was a trend towards higher incidence number of ulcer worsened without ES treatment (OR 0.38, 95% CI 0.12–1.24, $p=0.11$, $I^2=18\%$).

Adverse event

There was only one study reported adverse event in all eight trials. The authors indicated that some patients experienced minor and adverse reactions related to ES, which included red, raised, itchy skin beneath the large dispersive electrode. One patient had a persistent (>24h) red or burn under the active electrode, which was resolved in 48 hours, presumably from too high a stimulus intensity.

DISCUSSION

One of the most striking findings of the present review is the scarcity of updated prospective controlled studies about ES for PrU therapy in spinal cord injury population. A total of eight studies met inclusion criteria, majority of the studies were published over 10 years ago. The quality of the eight studies was generally poor. Of those 5 RCTs, only two trials were classified as good quality of evidence according to Jadad scale alongside using allocation concealment and intention to treat analysis. Other 3 RCTs and 3 Non-randomised controlled trials were classified as lower level of evidence with moderate to high risk of bias.

Based on the current available data, a meta-analysis of RCTs and non-RCTs showed an average higher daily healing rate during treatment period when patients received ES in adjunction to standard wound care. However, the higher daily healing rate in ES groups was not significant in pooled analysis of good quality of RCTs alone. Pooled analysis demonstrated that the numbers of ulcers completed healed was significantly higher in people receiving ES treatment than those without ES treatment. In addition, the incidence of ulcer worsened was insignificantly lower in ES treated group than control group.

Indeed, ES has been proposed as a therapeutic modality for wound healing over a century ago and has been well documented since the 1960's especially for wounds not responding to standard forms of treatment.^{9,25,26,27} Although the exact underline mechanism on how ES promote the healing of PrU remains unclear, theories of ulcer healing being enhanced by

functional ES have been established by numerous pre-clinical studies. It is known that endogenous electrical fields that are measurable electric potentials, naturally exist in human body and are known to be vital for tissue development and repair. The electrical potentials at the epidermis is known as ‘transepithelial potential’ that was generated by intact skin through directional active ion transportation, leading the concentration of negative chlorine ions at the surface and positive sodium and potassium ions in the tissues. The epithelial layer of intact skin acts as electrical barrier. When a wound occurs, the epithelial barrier is broken, it allows the current flows out of the wound. The transepithelial potential collapses and ions immediately begin to leak out, establishing a weak but measurable current between the skin and inner tissues, called the ‘current of injury’. The current is thought to continue until the skin defect is repaired.^{25,26,28} Application of an external electrical current to wounds is believed to mimics the body’s natural bioelectricity and restarts and stimulates endogenous electrical fields and as such promotes wound healing. The exogenous electrical currents have been shown to enhance the natural bioelectrical signals to promote ulcer healing in different ways. For instance, ES enhanced the process of angiogenesis and granulation through directing keratinocyte and fibroblast migration, increased collagen production, promoting fibroblast proliferation, and increased VEGF production. ES has also been demonstrated to enhance cellular activities such as collagen and DNA synthesis, ATP concentration, and generation of chemotaxis factors. Moreover, ES can increase tissue perfusion, decrease oedema, direct and accelerate the process of endothelial migration in the wound tissue and promote angiogenesis and galvanotaxis to enhance wound healing.^{9,28,29}

With regards to the stimulation mode, there were three types of electrical stimulation currents used in the studies within our review. The constant direct current that involves unidirectional continuous flow of current for longer than 1 second has been associated with antibacterial effect in PrU healing, but it can cause chemical and thermal burns.³⁰ This type of ES was employed by two studies in the review. The most commonly used ES for PrU healing in the review was the pulsed current that involves nonsinusoidal, interrupted current flow for a brief period of time. It is suggested that pulsed current ES more closely mimics the “current of injury” necessary for triggering tissue healing by sustained activation of the voltage-gated sodium channels in the surrounding tissues. As compared with continuous DC stimulation, pulsed current ES may carries a lower risk of possible skin burn and a greater depth of penetration.^{30,31} The pulsed current ES was utilised in seven out of eight studies. For stimulus

pulse settings, stimulation duration varies from 40Hz to 100 Hz in frequency, and 50–150 V or 4mA to 45mA in intensity. The other type of ES was alternating current, which is the continuous bidirectional flow of charged particles in which a change in direction of flow occurs at least once every second. To examine the effectiveness of different type of stimulation mode, we performed a meta-analysis of two trials investigating pulsed current in comparison of constant direct current or alternating current. Pooled analysis showed that pulsed current ES significantly improved daily healing rates compared with constant direct current or alternating current.

In terms of electrodes configuration, five studies employed the active electrode directly on the wound bed, the negative electrode was placed on the intact skin around the edge of the ulcer. Four studies employed the negative and positive electrodes on opposite sides of the pressure ulcer on the intact skin. One study compared electrodes configuration by either placing the active electrode in the wound and the dispersive electrode at a distance of ulcer versus placing both electrodes on the edge of ulcer. The electrode polarity has long been thought a complex issue. For example, anodal stimulation was shown to have greater antibacterial effects and increasing fibroblast migration^{32, 33} while cathode stimulation enhanced Keratinocyte migration²⁸ and increased fibroblast proliferation³². Nevertheless, it is recognised that the electrical field generated in former configuration is similar to the direction of the endogenous electrical field while the electrical field generated in the latter configuration is different from the endogenous electric field²⁶. In our review, although the average daily healing rate was significantly higher by ES active electrode overlaying the wound surface than both electrodes placed on the side of wound, this study was not RCTs and was classified as low level of evidence with high risk of bias. We cannot draw a definitive conclusion regarding the impact of electrode configuration.

STUDY LIMITATIONS:

Systematic reviews and meta-analysis always present a number of limitations. These include publication bias (particularly against negative findings), language restrictions, heterogeneity across each studies and coding of key words. Substantial heterogeneity in some analysis made us difficult to interpret those findings and draw firm conclusions. Heterogeneities can

be explained by the variation of study design and stimulation modes used across the studies in this review. Language restriction cannot be avoided in this review due to lack of interpretation resource. However, previous study indicated that trials reported in languages other than English are of lower methodological quality. Nevertheless, we adopted a well-structured search strategy that was approved by a clinical librarian, and supplemented all 'explode' functions and utilised hand searches as well as contacting specialists to minimise the potential bias.

CONCLUSION

The methodological quality of the studies included in this review was poor. Based on current available limited level 1 evidence, ES enhanced ulcer healing rate as an adjunctive therapy in SCI population. Pulsed direct current ES may confer better benefit for PrU healing than alternating or constant direct current. Future work is urgently needed in the form of well-designed clinical studies using large sample populations on determining the optimal stimulation location and stimulation parameters to confirm the beneficial effect on the enhancement of PU healing in SCI.

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